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MEMORANDUM

Subject: BLA STN 125197
Sipuleucel-T/Provenge®
OBE/DE Review for Pharmacovigilance Planning

To: Lori Tull, Regulatory Project Manager OCTGT/CBER

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Background

OBE/DE was asked by OCTGT to review the BLA for sipuleucel-T (Provenge®). The purpose of the review is to identify potential safety issues that might need to be addressed in a post-marketing pharmacovigilance plan if the product is licensed.

Sipuleucel-T (APC8015) is an autologous active cellular immunotherapy product designed to stimulate an immune response against prostate cancer. It consists of autologous peripheral blood mononuclear cells, including antigen presenting cells activated in vitro with a recombinant fusion protein, prostatic acid phosphatase (PAP) linked to granulocyte-macrophage colony-stimulating factor. The proposed indication for sipuleucel-T is treatment of men with asymptomatic metastatic androgen independent prostate cancer (AIPC).

When a new product is marketed, the exposed population usually differs quantitatively and qualitatively from the population studied in pre-approval trials. The number of patients exposed is much larger, usage generally expands to unlabeled indications, and exposed patients have a broader array of demographic features, co-morbid conditions, and concomitant medical product use. Postmarketing safety data collection is especially important when the product is a new molecular drug entity or a first-in-class biologic.

For most products, routine pharmacovigilance (i.e., compliance with applicable postmarket reporting requirements under FDA regulations) is sufficient for postmarketing risk assessment. As outlined in *Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment* (http://www.fda.gov/Cder/guidance/6359OCC.htm), FDA believes pharmacovigilance plans may be appropriate when: (1) serious safety risks have been

identified pre- or post-approval, or (2) at-risk populations have not been adequately studied. The pharmacovigilance plan is developed by a product's sponsor and is specifically focused on detecting new safety risks and/or evaluating already identified potential safety risks.

Pharmacovigilance Planning Recommendations for BLA STN 125197

These recommendations are based on information from the sponsor's assessment of the data as submitted in the BLA summaries. Additional and/or revised recommendations may be forthcoming after CBER clinical and statistical reviewers have evaluated the primary data. We are offering this preliminary review in order to allow the sponsor maximal time to develop a Pharmacovigilance Plan.

Outcomes in African American Patients

Ten African-American (AA) subjects received sipuleucel-T in the pivotal trials. As pointed out by the sponsor, this low number precludes an assessment of safety or efficacy in this population. The latest figures available from NCI's Cancer Statistics Review (2003) indicate that AA men have a higher annual incidence rate of invasive prostate cancer than Caucasian patients (247 vs. 160 per 100,000). It is generally accepted that the AA population also has a poorer prognosis, although one recent pooled analysis of 8 multi-institutional trials has shown that white men are at increased risk for death from hormone refractory prostate cancer relative to AA men[1]. The cause(s) for observed racial difference remains to be determined (ie. genetic factors, other tumor and /or patient characteristics, barriers to healthcare services, etc.[2, 3,4]).

Because it is questionable whether trial outcomes for Caucasian patients can be extrapolated to AA patients, we recommend that the sponsor begin now to develop a pharmacovigilance plan that might include a registry to capture disease characteristics, clinical status at enrollment, and race/ethnicity of consenting patients. Inclusion of identifiers (date of birth and SSN) would then allow assessment of survival using National Death Index data (www.cdc.gov/nchs/ndi.htm). In deciding whether to establish this registry, we recommend that the sponsor consider the following factors as set forth in the *Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment* guidance: 1) the types of additional risk information needed; 2) the attainability of that information through other methods; and 3) the feasibility of establishing the registry. The Guidance includes the components recommended for registry protocols and implementation.

Additional Potential Post-Marketing Safety Issues

Secondary hematologic malignancies: Table 37 in the safety summary includes one case of plasma cell malignancy among all patients in *completed* trials. Table 35 includes 2 entries of chronic myelomonocytic leukemia among 75 subjects in an *on-going* trial. I was unable to locate a summary number of all patients under study who were diagnosed in the follow-up period with hematologic malignancies. Given the small number of patients exposed to the product, this finding may be an important signal, especially since one of its components is a stimulating factor for myeloid cells (GMCSF), and the product has been shown by the sponsor to stimulate the proliferation of T cell hybridomas in vitro. On the other hand, the grim prognosis of the proposed indication renders this concern of questionable clinical importance. However, if the product is licensed, it is very likely to be used in patients with a better prognosis for long-term survival. In

that scenario, a secondary hematologic malignancy assumes great practical importance. Pending the results of OCTGT/Biostatistics review of the primary data, it may be advisable to include secondary hematologic malignancies in the Pharmacovigilance Plan. We can work with the sponsor to identify the most efficient way to accomplish this goal, perhaps via an educational program for oncologists regarding the importance of reporting this adverse event to the sponsor and/or Medwatch. Guidance for such programs can be found at www.fda.gov/cder/guidance/6358fnl.pdf.

Stroke: According to the sponsor, 14 subjects experienced a CVA among the 669 patients in the safety population, with no significant difference between the product and the placebo arms. However, there was no arm for comparison where patients did not undergo leukopheresis. As noted by the sponsor, the subjects were at risk of stroke due to age-related conditions and the underlying metastatic malignancy. In addition, 6 of the 7 strokes in the pivotal trials occurred at least 3 months after the last infusion. Nonetheless, given the small number of studied patients, this may be an early signal of a problem that could emerge if the product is licensed and then used in large numbers of patients with a better prognosis for extended survival. If this product is approved and the adverse event is included in the labeling, FDA will not receive spontaneous reports of these serious events in "real-time" according to the regulations. Instead, we will receive them in quarterly periodic reports for the first 3 years and then annually. We would suggest that FDA ask the sponsor to consider all thromboembolic events (6 of the 7 CVAs in pivotal trials were thrombotic) to be reportable under the regulations for 15-day expedited reporting, a request that is consistent with existing adverse event reporting regulations.

Sepsis: The total number of patients who developed sepsis in the sponsor's studies for this product awaits detailed review by the clinical team, but 4 of the 7 discontinued patients in pivotal trials had sepsis. Since there was no arm where patients did not undergo the leukopheresis procedure, we suggest that all infectious AE be reported to FDA under the regulations for expedited reporting, for the same reasons set forth in the previous section (stroke).

Conclusion

We recommend that the sponsor be asked to develop and submit a pharmacovigilance plan for Provenge® that addresses the issues covered in this review and any others that they or the OCTGT review team identify. We encourage the sponsor to discuss development plans with FDA at the earliest possible date.

References

1. Halabi S et al. Clinical outcomes by age in men with hormone refractory prostate cancer: a pooled analysis of 8 CALGB studies. 2006 J Urol 176:81-6.
2. Berger AD et al. Differences in clinicopathologic features of prostate cancer between black and white patients treated in the 1990s and 2000s. 2006 Urology 67:120-4
3. Cohen JH et al. Racial differences in clinical progression among Medicare recipients after treatment for localized prostate cancer. 2002 Cancer Causes Control 17:803-11.
4. Nielson ME et al. Black race does not independently predict adverse outcome following radical retropubic prostatectomy at a tertiary referral center. 2006 J Urol 176:515-9.